

### **REMARKS**

The October 20, 2004 Office Action rejects claim 8 under 35 U.S.C. § 112, second paragraph as being indefinite because of the use of the tradename “EUDRAGIT.” In response, claim 8 has been amended to refer to “an anionic polymer based on methacrylic acid esters.” This identity of EUDRAGIT polymers would be known or readily ascertainable to persons having ordinary skill in the art. For example, EUDRAGIT is disclosed as such in the attached publicly available product literature (obtained from the internet at <<[http://www.roehm.de/en/pharmapolymers?content=/en/pharmapolymers/formulation/enteric/enteric\\_list](http://www.roehm.de/en/pharmapolymers?content=/en/pharmapolymers/formulation/enteric/enteric_list)>> (under the link to “Basic Information”); last accessed November 30, 2004). With this amendment, applicants submit that claim 8 is now in condition for allowance.

The October 20, 2004 Office Action indicates the allowability of claims 1-7 and 9-22. Upon review, applicants note that there is a typographical error in claim 22, which is corrected with this amendment. This correction is supported throughout the specification, for example at paragraph [0011]. Claim 6 is also amended to correct a spelling error. Applicants submit that the amendment of claims 6 and 22 are not related to patentability and do not limit the original scope of the claims.

### **CONCLUSION**

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the

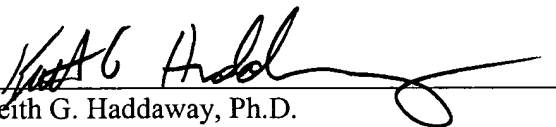
Applicants: LULLA et al.  
Appl. No.: 10/686,528

outstanding Office Action and, as such, the present application is in condition for allowance. Applicants thus request that a Notice of Allowance indicating the allowability of claims 1-22 be issued. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is hereby invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment is respectfully requested.

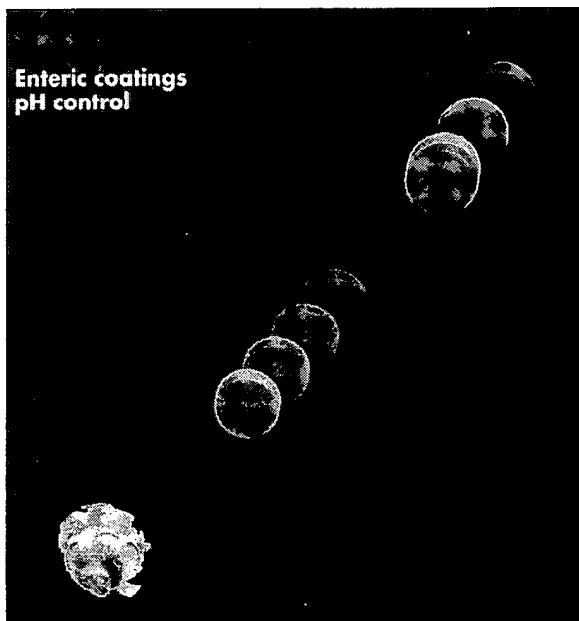
Respectfully submitted,

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*Röhm Pharma Polymers*

## Enteric Coatings-pH control with EUDRAGIT®



Enteric coatings  
pH control

### Introduction:

Many pharmaceutical dosage forms irritate the stomach due to their chemical properties. Others undergo chemical changes in gastric acid and through the action of enzymes.

Specific EUDRAGIT® acrylic polymers have been developed for peroral dosage forms with step-wise release of active ingredients in the digestive tract. The pharmaceutical principle: reliable EUDRAGIT® coatings soluble as a function of environmental pH value.

Depending on the pharmaceutical or technical objective, different EUDRAGIT® polymers offer optimal solutions:

### Coatings which dissolve at rising pH values:

- Release of active ingredients in the duodenum with EUDRAGIT® L 100-55 or the aqueous dispersion EUDRAGIT® L 30 D-55 at pH values over 5.5.
- Release of active ingredients in the jejunum to ileum with EUDRAGIT® L 100 at pH values over 6.0 or with mixtures of EUDRAGIT® L 100 and EUDRAGIT® S 100 in a pH range from 6.0 to 6.5.
- Release of active ingredients near the colon with EUDRAGIT® S 100 in a pH range from 6.5 to 7.5.

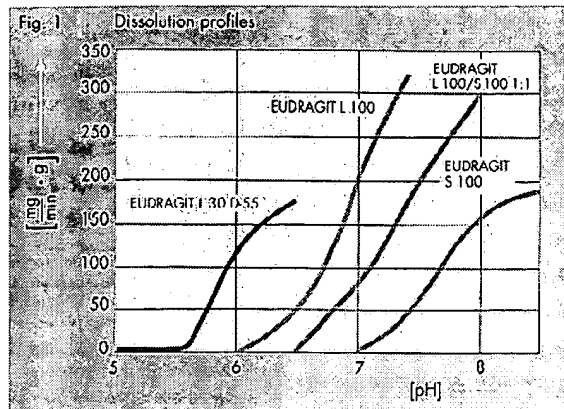
### Products

#### EUDRAGIT® L and EUDRAGIT® S

grades are anionic polymers based on methacrylic acid esters. The films are insoluble below pH 5 and thus resistant to gastric fluid. By salt formation in the neutral to weakly alkaline medium of intestinal fluid, the films dissolve step-wise at pH values above 5.5.

## Product properties

Of decisive importance for the controlled release of enteric-coated active ingredients is the dissolution profile of the EUDRAGIT® L/S film formers in the intestinal pH range from 5.5 to 7.0. The graph in Fig. 1 indicates how the film coatings dissolve in the intestine. In the duodenum, a pH range of 5.5 - 6.0 is to be expected; in the lower sections of the intestine, the pH value normally increases gradually to about pH 6.5 - 7.0 near the colon. However, the release of active ingredients also depends on the thickness of the film coatings and the solubility characteristics of the active ingredient under physiological conditions.



All polymer types in Fig. 1 can be mixed with each other in any desired ratio, thus making it possible to adjust intermediate values. The release values established in vitro must be confirmed in pharmacological and clinical tests.

## Application

EUDRAGIT® polymers can be applied as coatings to all conventional, solid oral dosage forms such as tablets, capsules, small particles. These polymers can also be used to manufacture pellets, granules and sustained-release tablets.

### Polymers processed form

- Solution in organic solvents (alcohols, acetone)
- Mixtures of organic solutions with water
- Purely aqueous latex dispersions

The coatings can also be processed with ease in all film-coating or fluidized-bed equipment that is commonly used worldwide.

### Further possible applications

EUDRAGIT® L/S coatings show an excellent sealing effect even at very thin layers. This enables the following technical effects to be obtained:

- Protection against atmospheric humidity
- Isolating mutually incompatible particles in combination products
- Masking of cores with an unpleasent odour or taste
- Granulation of active ingredients in powder form

The sealing effect of the film coatings naturally increases in proportion to the film thickness. In that case however, the release of active ingredients in digestive fluids with a pH of less than 5 is also delayed. Compromises can, however, be found.

## Basic formulations for organic polymer solutions

EUDRAGIT® L/S solid substances can be dissolved with ease in alcohols and acetone, providing solutions of about 10 - 15%.

The addition of plasticizers and glidants is a must in order to ensure sufficient elasticity of the films and to reduce as much as possible the tendency of the cores to stick together during the processing.

When manufacturing EUDRAGIT® solutions, the regulations for handling flammable solvents must be observed. All processing equipment must be observed. All processing equipment must be explosion-proof. To avoid the risk of toxicity, workplaces must be properly ventilated and contaminated air extracted. The working equipment must be earthed.

### I. Basic formulation for a colorless enteric coating

Sufficient for approx. 12 kg cores of average size.  
(Ø 8 mm, 200 mg in weight or  
approx. 3 - 5 kg pellets (Ø 0.5 - 1.2 mm))

<b>EUDRAGIT® L/S 100</b>	600 g
Triethyl citrate	60 g
Talc	300 g
Water	500 g
Isopropyl alcohol	8,540 g
	<b>10,000 g</b>
Solids content:	9.6%
Polymer content:	6.0%

Pigments can be incorporated in the formulation. Suitable pigments are titanium dioxide as a white pigment and food colour lakes based on aluminium oxide or iron oxide pigments. It contains 20% polyethylene glycol on polymer. To obtain a plasticizing effect, 10% is usually sufficient. The higher concentration given here additionally provides a gloss-enhancing effect.

### II. Formulation for colored final coats on enteric coated preparations

Sufficient for approx. 25 kg cores of average size.  
(Ø 8 mm, 200 mg in weight) or  
approx. 10 - 20 kg pellets (Ø 0.5 - 1.2 mm)

<b>Polymer solution</b>	
<b>EUDRAGIT® L/S 100</b>	250 g
Solvent	7,250 g
<b>Pigment suspension</b>	
Polyethylene glycol 6000	50 g
Talc	400 g
Titanium dioxide / pigments	300 g
Water	100 g
Isopropyl alcohol	1,650 g
	<b>10,000 g</b>
Solids content:	10.0%
Polymer content:	2.5%

### III. Formulation for full-colored enteric coatings

Sufficient for approx. 12 kg cores of average size.  
(Ø 8 mm, 200 mg in weight) or  
approx. 3 - 5 kg pellets (Ø 0,5 - 1,2 mm)

#### Polymer solution

<b>EUDRAGIT L/S 100</b>	625 g
Solvent	8,125 g

#### Pigment suspension

Polyethylene glycol 6000	65 g
Talc	190 g
Titanium dioxide / pigments	125 g
Water	130 g
Isopropyl alcohol	740 g
	<b>10,000 g</b>

Solids content:	10.1%
Polymer content:	6.3%

### Aqueous dispersions

Aqueous coating formulations can be prepared by stirring the EUDRAGIT® powder into water and adding alkali.

### IV. Basic formulation for colorless enteric coatings.

Sufficient for approx. 35 kg cores of average size  
(Ø 8 mm, 200 mg in weight) or  
approx. 10 - 15 kg pellets (Ø 0.5 - 1.2 mm)

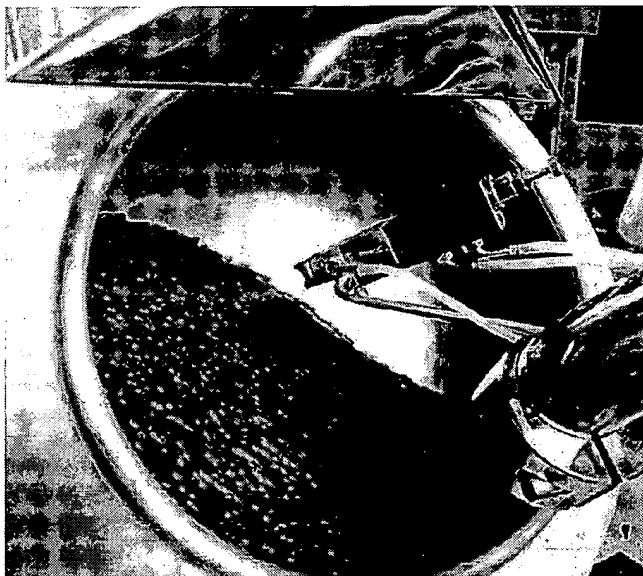
#### Redispersion

<b>EUDRAGIT L 100-55</b>	1,755 g
4% NaOH (1 N) solution	585 g
Water	3,510 g

#### Pigment suspension

Triethyl citrate	175 g
Glycerol monostearate	35.9 g
Water	3,940 g
	<b>10,000 g</b>

Solids content:	19.9%
Polymer content:	17.6%



When manufacturing full-colored enteric film coatings, the ratio of pigments to titanium dioxide can be varied as a function of the desired intensity of colour. The quantities given in formulation VI provide a uniform colour coat on white tablet cores.

#### V. Formulation for colored final coats on enteric-coated preparations

Sufficient for approx. 50 kg cores of average size (Ø 8 mm, 200 mg in weight) or approx. 25 kg pellets (Ø 0.5 -1.2 mm)

#### Polymer dispersion

<b>EUDRAGIT® L 30 D-55</b>	1,670 g
Water	3,335 g

#### Pigment suspension

Triethyl citrate	50 g
Talc	830 g
Titanium dioxide / pigments	500 g
Sodium carboxymethyl-cellulose	35 g
Polyethylene glycol 6000	80 g
Water	3,500 g
	<b>10,000 g</b>

Solids content:	20.0%
Polymer content:	5.0%

#### VI: Formulation for full-colored enteric coatings

Sufficient for approx. 30 kg cores of average size (Ø 8 mm, 200 mg in weight) or approx. 10 - 15 kg pellets (Ø 0.5 -1.2 mm)

#### Polymer dispersion

<b>EUDRAGIT® L 30 D-55</b>	4,710 g
Water	1,755 g

#### Pigment suspension

Triethyl citrate	140 g
Talc	640 g
Titanium dioxide / pigments	175 g
Sodium carboxymethyl-cellulose	55 g
Polyethylene glycol 6000	55 g
Water	2,470 g
	<b>10,000 g</b>

Solids content:	24.8%
Polymer content:	14.1%

If more intensive colour is required and tablets of perhaps uneven colour are to be entirely covered, the quantity of white and coloured pigments must be increased. In that case, it may be advisable to first apply a colourless enteric base coat and then intensively coloured polymer layer.

#### VII: Formulation for enteric coatings with delayed dissolution in intestinal fluid

Sufficient for approx. 30 kg cores of average size (Ø 8 mm, 200 mg in weight) or approx. 10 - 15 kg pellets (Ø 0.5 - 1.2 mm)

Recommended post stirring time after the addition of the plasticiser: 1 hours

#### Redispersion

<b>EUDRAGT® S 1 00</b>	1,440 g
1.7% ammonia solution	731 g
Triethyl citrate	720 g
Water	4,306 g

#### Pigment suspension

Glycerol monostearate	43 g
Water	2,760 g
	<b>10,000 g</b>

Solids content:	22.2%
Polymer content:	14.4%



### VIII: Formulation for enteric coatings with delayed dissolution in intestinal fluid

Sufficient for approx. 30 kg cores of average size (Ø 8 mm, 200 mg in weight) or approx. 10 - 15 kg pellets (Ø 0.5 - 1.2 mm)

Recommended post stirring time after the addition of the plasticiser: 16 hours

#### Redispersion

<b>EUDRAGIT® S 100</b>	1,440 g
KOH, 1N solution	734 g
Triethyl citrate	720 g
Water	4,306 g

#### Pigment suspension

Glycerol monostearate	43 g
Water	2,757 g
	<b>10,000 g</b>

Solids content:	22.4%
Polymer content:	14.4%

## Excipients

### Plasticizer

Films of EUDRAGIT® tend to become brittle (cracking) below 10%. To improve the elasticity up to 25% can be added. EUDRAGIT® L 100 and EUDRAGIT® S 100 in aqueous formulations require a much higher proportion of plasticizer (40 - 50%). In all formulations, triethyl citrate has proved its worth as a plasticizer.

### Solvents

Acetone and alcohols are preferentially used for manufacturing polymer solutions. An overview of the average dissolution time in minutes for the most common solvents or solvent / water mixture shows the following table.

Solvent	EUDRAGIT® L 100-55	EUDRAGIT® L 100	EUDRAGIT® S 100
Methanol	10	15	30
Methanol / water 97:3	10	15	25
Ethanol	20	10	10
Ethanol/water 97:3	20	10	25
Ethanol/water 6:4	20	20	40
Isopropyl alcohol	30	40	35
Isopropyl alcohol / water 97:3	20	15	20
Isopropyl alcohol / water 6:4	20	25	45
n-Butanol	30	70	swelled
Acetone	35	15	10
Acetone / water 97:3	15	25	10
Acetone / water 6:4	15	15	swelled
Acetone / isopropyl alcohol 4:6	-	30	5



### Glidants

Polymer solutions and dispersions go through a tacky phase during drying. To avoid agglomeration of the cores, glidants are added to the spray suspensions. At critical points of manufacture, these can also be added in the form of a powder.

- Talc and Kaolin are often used in combination with pigments.
- Glycerol monostearate e. g. Imwitor® 900 is a good alternative to talc as a glidant in all the aqueous formulations mentioned.
- Micronised silic acid can be used in quantities of 10-30% on polymer and does have a matting effect and increases the permeability of film coatings.
- Magnesium stearate is somewhat more effective than talc and often provides good sealing of the film coatings and low permeability. However, it can only be used in organic polymer solutions, since coagulation or thickening may occur in aqueous dispersions.
- Pigments for film coating processes, both so-called aluminium colour lakes and iron oxides are suitable. Watersoluble dyes usually lead to inhomogeneous colouring of the coatings, which moreover rub off during handling.
- Titanium dioxide, apart from adjusting the intensity of the coatings, which moreover rub off during handling.

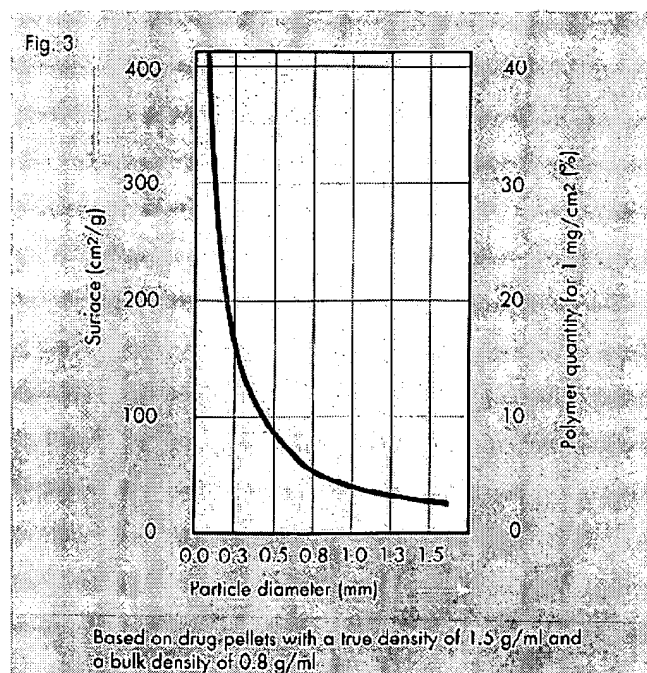
## The Process

EUDRAGIT® polymethacrylates can be processed in all conventional types of coating equipments, by all coating operation commonly performed in the pharmaceutical industry. Coating pans with spraying devices and high drying air capacity are particularly suitable for tablets. Fluid-bed coaters are preferred for small particles, which show a more pronounced tendency to agglomeration.

### Suggestions for processing

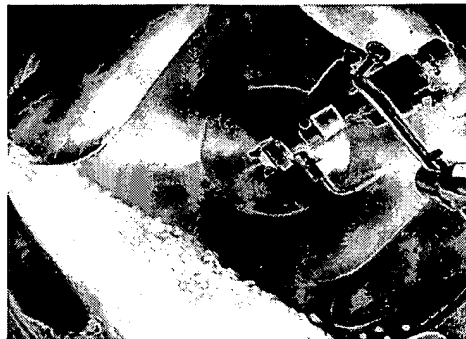
#### Quantities to be applied

For enteric coatings, 4 to 6 mg polymer are applied per cm<sup>2</sup> of tablet surface, or 10 to 30 per cent by weight on particles such as pellets, granules or crystals with sizes in the range of about 0.5 to 1.5 mm. The required polymer quantity may vary according to surface structure, mechanical stability or solubility of the dosage form to be coated.



### Pan process

A maximum of air should be introduced to ensure rapid drying of the sprayed solution. In order to reduce attrition during rotation or fluidisation to a minimum, cores of adequate stability have to be used. Inclusion of a substantial amount of fines increases the permeability of the film coats and may result in loss of enteric properties.



Abrasion of the applied films, especially along tablet bands, is also to be avoided. It can damage the film coatings.

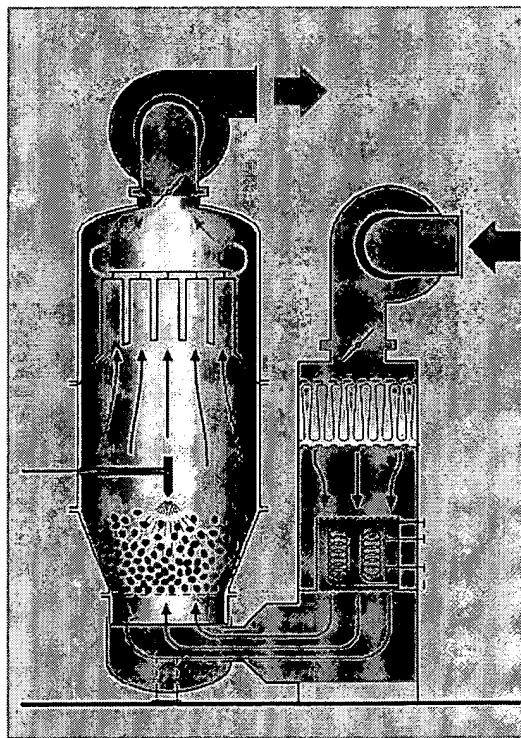
The spray rate has to be adjusted in such a way that spraying is performed more or less continuously and simultaneously with adequate drying.

Because of the high atomization pressure to which spray suspensions are exposed in airless spray systems, a certain minimum spray rate is required, which permits continuous spraying only from batch sizes of 80- 100 kg onwards.

### Fluidized-bed processes

Fluidized-bed processes are mainly used for the coating of small particles. Because of the much higher throughput of drying air in comparison with other coating operations, spraying is faster and the agglomeration tendency less pronounced. Since particles have a much larger specific surface than tablets, the overall coating requirement in per cent is higher.

To facilitate assessment of polymer requirement, measurement of the product surface area is recommended. Simple measurements of surface area can be performed by means of a Blaine apparatus or modified Friedrichs manometer.



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